What is Claimed is:

1. A compound which has the structure

$$\begin{array}{c|c}
R^{2a} & R^{2b} \\
R^{2a} & R^{2a} \\
R^$$

5

10

15

20

wherein x is 1,2, 3 or 4; m is 1 or 2; n is 1 or 2;

Q is C or N;

A is O or S;

Z is O or a bond;

R¹ is H or lower alkyl;

X is CH or N;

 ${\ensuremath{\mbox{R}}}^2$ is H, alkyl, alkoxy, halogen, amino or substituted amino;

 R^{2a} , R^{2b} and R^{2c} are the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

R³ is H, alkyl, arylalkyl, aryloxycarbonyl, alkyloxycarbonyl, alkynyloxycarbonyl, alkenyloxycarbonyl, arylcarbonyl, alkylcarbonyl, aryl, heteroaryl, alkyl(halo)aryloxycarbonyl, alkyloxy(halo)aryloxycarbonyl cycloalkylaryloxycarbonyl, cycloalkyloxyaryloxycarbonyl, cycloheteroalkyl, heteroarylcarbonyl, heteroaryl-heteroarylalkyl, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxycarbonylamino,

aryloxycarbonylamino, heteroaryloxycarbonylamino, heteroaryl-heteroarylcarbonyl, alkylsulfonyl, alkenylsulfonyl, heteroaryloxycarbonyl, cycloheteroalkyloxycarbonyl, heteroarylalkyl, aminocarbonyl, substituted aminocarbonyl,

alkylaminocarbonyl, arylaminocarbonyl, heteroarylalkenyl, cycloheteroalkylheteroarylalkyl, hydroxyalkyl, alkoxy, alkoxyaryloxycarbonyl, arylalkyloxycarbonyl, alkylaryloxycarbonyl, arylheteroarylalkyl, arylalkylarylalkyl, aryloxyarylalkyl, alkynyloxycarbonyl,

25.

30

haloalkoxyaryloxycarbonyl, alkoxycarbonylaryloxycarbonyl, aryloxyaryloxycarbonyl, arylsulfinylarylcarbonyl, arylthioarylcarbonyl, alkoxycarbonylaryloxycarbonyl, arylalkenyloxycarbonyl, heteroaryloxyarylalkyl,

- aryloxyarylcarbonyl, aryloxyarylalkyloxycarbonyl, arylalkenyloxycarbonyl, arylalkylcarbonyl, aryloxyalkyloxycarbonyl arylalkylsulfonyl, arylthiocarbonyl, arylalkenylsulfonyl, hateroarylsulfonyl, arylsulfonyl, alkoxyarylalkyl,
- 10 heteroarylalkoxycarbonyl, arylheteroarylalkyl, alkoxyarylcarbonyl, aryloxyheteroarylalkyl, heteroarylalkyloxyarylalkyl, arylarylalkyl, arylalkenylarylalkyl, arylalkoxyarylalkyl, arylcarbonylarylalkyl, alkylaryloxyarylalkyl,
- arylalkoxycarbonylheteroarylalkyl, heteroarylalkyl, arylalkoxycarbonylheteroarylalkyl, heteroarylalkyl, arylalkenylheteroarylalkyl, arylaminoarylalkyl or aminocarbonylarylarylalkyl;

Y is CO_2R^4 (where R^4 is H or alkyl, or a prodrug ester) or Y is a C-linked 1-tetrazole, a phosphinic acid of the structure P(O) (OR^{4a}) R^5 , (where R^{4a} is H or a prodrug ester, R^5 is alkyl or aryl) or a phosphonic acid of the structure P(O) (OR^{4a})₂, (where R^{4a} is H or a prodrug ester);

including all stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof, with the proviso that where X is CH, A is O, Q is C, Z is O and Y is CO_2R^4 , then R^3 is other than H or alkyl containing 1 to 5 carbons in the normal chain.

2. A compound having the structure

or

10

15

3. The compound as defined in Claim 1 having the structure

4. The compound as defined in Claim 1 having structure

$$(CH_2)_x O X (CH_2)_m N (CH_2)_n CO_2R^4$$
or

5. The compound as defined in Claim 1 wherein $(CH_2) \times is$ alkylene, alkenylene, allenyl, or alkynylene.

6. The compound as defined in Claim 4 wherein \boldsymbol{X} is CH.

7. The compound as defined in Claim 4 wherein X $\,$ 20 $\,$ is N.

15

8. The compound as defined in Claim 1 having the structure

$$\begin{array}{c|c} & & & \\ & &$$

wherein R¹ is alkyl, R^{3b} is arylalkylamino, aryl-5 arylamino, arylamino, alkoxyarylamino, dialkoxyarylamino, dihaloarylamino or alkylthioarylamino.

9. The compound as defined in Claim 1 having the structure

$$(CH_2)_x O R^1$$

$$(CH_2)_x O R^3$$

$$(CH_2)_n - CO_2H$$

10. The compound as defined in Claim 1 wherein ${\ensuremath{\mathsf{R}}}^{2a}$ is alkoxy or H,

(CH₂)_x is CH₂, (CH₂)₂, (CH₂)₃, or CH₃, (CH₂)_m is CH₂, or CH₂ (Where R_a is alkyl or alkenyl), (CH₂)_n is CH₂, R¹ is lower alkyl, preferably -CH₃, R² is H, R^{2a} is H, R⁴ is H, X is CH, and R³ is arylalkyloxycarbonyl, arylaekyl, aryloxyarylalkyl, arylakyl, aryloxycarbonyl, haloaryl-oxycarbonyl,

- 20 alkoxyaryloxycarbonyl, alkylaryloxycarbonyl, aryloxyaryloxycarbonyl, heteroaryloxyarylalkyl, heteroaryloxycarbonyl, aryloxyarylcarbonyl, arylalkenyloxycarbonyl, cycloalkylaryloxycarbonyl, arylalkylarylcarbonyl, heteroaryl-heteroarylalkyl,
- 25 cycloalkyloxyaryloxycarbonyl, heteroarylheteroarylcarbonyl, alkyloxyaryloxycarbonyl,
 arylalkylsulfonyl, arylalkenylsulfonyl, alkoxyarylalkyl,
 arylthiocarbonyl, cycloheteroalkylalkyloxycarbonyl,
 cycloheteroalkyloxycarbonyl, or polyhaloalkylaryloxy-
- 30 carbonyl, which may be optionally substituted.

10

- 11. The compound as defined in Claim 5 wherein ${\tt X}$ is CH.
- 5 12. The compound as defined in Claim 5 wherein \boldsymbol{X} is \boldsymbol{N} .
 - 13. The compound as defined in Claim 1 wherein \times is 2, m is 1, and n is 1.
 - 14. The compound as defined in Claim 1 having the structure

$$\begin{array}{c|c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & &$$

15. The compound as defined in Claim 1 having the structure

$$CH_2CH_2$$
 or CH_2 CH_2 CO_2H

where $(CH_2)_n$ is CH_2 or CH_3

10

16. The compound as defined in Claim 1 having the structure $% \left(1\right) =\left(1\right) ^{2}$

$$\begin{array}{c} Ph \\ \searrow N \\ CH_3 \end{array}$$

Ph
$$CO_2H$$
 CO_2H R^3 CO_2H R^3 R

10

10 15

- 331 -

, where $R^3 =$

15

10

$$Ph$$
 CO_2H
 R^{3c}
, where R^{3c} =

10

15

(S)-CH₃, (R)-CH₃, (R) (R)

$$\begin{array}{c} Ph \\ CH_3 \end{array}$$

$$\begin{array}{c} Ph \\ CH_3 \end{array}$$

$$\begin{array}{c} Ph \\ CO_2H \end{array}$$

$$\begin{array}{c} Ph \\ CO_2H \end{array}$$

$$\begin{array}{c} \mathsf{Ph} \\ \mathsf{CH}_3 \end{array} \\ \begin{array}{c} \mathsf{OCH}_3 \end{array} \\ \begin{array}{c} \mathsf{Ph} \\ \mathsf{CH}_3 \end{array} \\ \begin{array}{c} \mathsf{O} \\ \mathsf{CH}_3 \end{array} \\ \begin{array}{c} \mathsf{O} \\ \mathsf{CH}_3 \end{array} \\ \begin{array}{c} \mathsf{OCHF}_2 \\ \mathsf{CO}_2\mathsf{H} \end{array}$$

$$\begin{array}{c} Ph \\ O \\ CH_3 \end{array} \begin{array}{c} O \\ O \\ CO_2H \end{array} \begin{array}{c} Ph \\ O \\ CH_3 \end{array} \begin{array}{c} O \\ O \\ CH_3 \end{array} \begin{array}{c} O \\ CO_2H \end{array} \begin{array}{c} O \\ O \\ CO_2H \end{array}$$

$$\mathbb{R}^{3d}$$
 \mathbb{R}^{N}
 \mathbb{C}_{H_3}
 \mathbb{R}^{3d}
 \mathbb{C}_{H_3}
 \mathbb{R}^{3d}
 \mathbb{R}^{3d}
 \mathbb{R}^{3d}
 \mathbb{R}^{3d}
 \mathbb{R}^{3d}

10

15

.OCH₃

- 337 -

5

CF3 F CI OCF3 F

CH₃, CH₃, CH₃, CF₃, CH₃, CH

Ph CH_3 CO_2H CO_2H CO_2H

10

10

CH₃ CH₃

CH₃, F, CH₃, F, SCH₃, CH₃, CH

10

Ph
$$CO_2H$$
 R^{3f} , where R^{3f} =

HN OCH3 HN CI HN SCH3

15

Ph
$$O = R^{3g}$$
 CO_2H , where $R^{3g} =$

CH₃, CH₃, CI, CI, CI, CI,

Ph CO_2H O_2S R^{3g} where R^{3g} =

15

CH₃, CH

CF₃, CH₃, F,

CH₃ CCF₃, CCF₃,

Ph N CO₂H

Ph CO₂H

where $R^3 =$

where $R^3 =$

, where R³ =

15

15

$$\begin{array}{c} Ph \\ \longrightarrow \\ O \\ \longrightarrow \\ CH_3 \end{array}$$

 $\dot{C}H_3$ \dot{R}^{3h} , where R^{3h} =

 \mathbb{R}^{3h} Ph

O

O

O

O

CH₃

, where \mathbb{R}^{3h} =

ĊНз

where $R^a = (\pm) - Me$, (\pm) n-Bu,

5

10

10

$$\begin{array}{c|c} Ph & & & \\ \hline \\ N & & \\ \hline \\ O & & \\ \hline \\ CH_3 & \\ \end{array}$$

$$\begin{array}{c|c} CH_3 & CH_3 \\ \hline \\ Ph & O & O \\ \hline \\ N & CO_2H \\ \hline \\ \end{array}$$

ọCH₃ OCH3 OCH₃ CH₃ CH₃ CH₃ ḖH₃ CH₃ CH₃

10

Ě CH₃

ÓCH3

$$\begin{array}{c|c} \mathsf{Ph} & & \mathsf{N} & \mathsf{CO}_2\mathsf{H} \\ \mathsf{N} & & \mathsf{O} & \mathsf{O} \\ \mathsf{O} & & \mathsf{O} \\ \mathsf{OCH}_3 & & \mathsf{OCH}_3 \\ \end{array}$$

$$\begin{array}{c|c} \mathsf{Ph} & & \mathsf{N} & \mathsf{CO_2H} \\ \\ \mathsf{N} & & \mathsf{O} & \mathsf{O} \\ \\ \mathsf{OCH_3} & & \mathsf{OCH_3} \\ \end{array}$$

17. The compound as defined in Claim 1 having the structure

$$\begin{array}{c} Ph \\ O \\ CH_3 \end{array}$$

$$\begin{array}{c} O \\ CH_3 \end{array}$$

18. The compound as defined in Claim 1 having the structure $\ensuremath{\text{18}}$

10

5

$$\begin{array}{c|c} & \text{OCH}_3 \\ & & \\ & & \\ \text{Ph} & & \\ &$$

OCH₃

Ph—N CO₂H

 $19. \ \ \,$ The compound as defined in Claim 1 having the $\, 5 \, \,$ structure

 $20\,.$ The compound as defined in Claim 1 having the 10 $\,$ structure

$$\begin{array}{c} Ph \\ O \\ CH_{3} \end{array}$$

$$\begin{array}{c} O \\ O \\ CH_{3} \end{array}$$

$$\begin{array}{c} O \\ O \\ CH_{3} \end{array}$$

$$\begin{array}{c} O \\ CD_{2}H \\ O \\ CH_{3} \end{array}$$

$$\begin{array}{c} O \\ CD_{2}H \\ O \\ CH_{3} \end{array}$$

$$\begin{array}{c} O \\ CD_{2}H \\ O \\ CH_{3} \end{array}$$

$$\begin{array}{c} O \\ CD_{2}H \\ O \\ CH_{3} \end{array}$$

$$\begin{array}{c} O \\ CD_{2}H \\ O \\ CH_{3} \end{array}$$

$$\begin{array}{c} O \\ CH_{3} \end{array}$$

$$\begin{array}{c} O \\ CD_{2}H \\ O \\ CH_{3} \end{array}$$

$$\begin{array}{c} O \\ CD_{2}H \\ O \\ CH_{3} \end{array}$$

$$\begin{array}{c} O \\ CD_{2}H \\ O \\ CD_{2}H \end{array}$$

$$\begin{array}{c} O \\ CD_{2}H \\ O \\ CD_{2}H \end{array}$$

$$\begin{array}{c} O \\ CD_{2}H \\ O \\ CD_{2}H \end{array}$$

$$\begin{array}{c|c} Ph & & & \\ \hline O & & & \\ \hline CH_3 & & & \\ \end{array}$$

$$\mathsf{Ph} \overset{\mathsf{O} \leftarrow \mathsf{CH}_3}{\underset{\mathsf{CO}_2\mathsf{H}}{\mathsf{H}}}$$

Ph-OCH3 OCF3

CH3

QCH₃

 $\mathsf{Ph} \overset{\mathsf{O} \longrightarrow \mathsf{CH}_3}{\mathsf{N}} \overset{\mathsf{N} \longrightarrow \mathsf{CO}_2\mathsf{H}}{\mathsf{O}} \overset{\mathsf{CO}_2\mathsf{H}}{\mathsf{O}} \overset{\mathsf{CO}_2\mathsf{H}} \overset{\mathsf{C}}{\mathsf{O}} \overset{\mathsf{$

ĊO₂H

$$0 \xrightarrow{\mathsf{CH}_3} N \xrightarrow{\mathsf{CO}_2\mathsf{H}} 0 \xrightarrow{\mathsf{OCH}_3}$$

 $Ar = CI \xrightarrow{OCH_3} OCH_3$ $OCH_3 OCH_3 OCH$

 $\,$ 21. The compound as defined in Claim 1 having the $\,$ 5 $\,$ structure

22. The compound as defined in Claim 1 having the structure

10

23. The compound as defined in Claim 1 having the structure

24. The compound as defined in Claim 1 having the structure

 $\,$ 25. The compound as defined in Claim 1 having the structure

10

5

26. The compound as defined in Claim 1 having the structure

 $\,$ 27. The compound as defined in Claim 1 having the structure

5

28. The compound as defined in Claim 1 having the structure

10

29. The compound as defined in Claim 1 having the structure

30. 15 structure

The compound as defined in Claim 1 having the $\frac{Ph}{CO_2H}$

5

31. The compound as defined in Claim 1 having the structure

32. The compound as defined in Claim 1 having the structure

- 10 33. A pharmaceutical composition comprising a compound as defined in Claim 1 and a pharmaceutically acceptable carrier therefor.
 - 34. A method for lowering blood glucose levels which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.
- 35. A method for treating diabetes which
 20 comprises administering to a patient in need of treatment
 a therapeutically effective amount of a compound as
 defined in Claim 1.
- 36. A method for treating a premalignant disease, an early malignant disease, a malignant disease, or a dysplastic disease, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

- 37. A pharmaceutical combination comprising a compound as defined in Claim 1 and a lipid-lowering agent, a lipid modulating agent, an antidiabetic agent, an anti-obesity agent, an antihypertensive agent, a platelet aggregation inhibitor, and/or an antiosteoporosis agent.
- 38. The pharmaceutical combination as defined in Claim 37 comprising said compound and an antidiabetic agent.
- 39. The combination as defined in Claim 38 wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPARα
 15 agonist, a PPAR γ agonist, a PPAR α/γ dual agonist, an SGLT2 inhibitor, a DP4 inhibitor, an aP2 inhibitor, an insulin sensitizer, a glucagon-like peptide-l (GLP-l), insulin and/or a meglitinide.
- 40. The combination as defined in Claim 39 wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, Gl-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 and/or NVP-DPP-728A.
- 41. The combination as defined in Claim 38 wherein the compound is present in a weight ratio to the antidiabetic agent within the range from about 0.001 to about 100:1.
- 35 42. The combination as defined in Claim 37 wherein the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake

20

inhibitor, a thyroid receptor agonist, an aP2 inhibitor and/or an anorectic agent.

- 43. The combination as defined in Claim 42 wherein the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol.
- 10 44. The combination as defined in Claim 37 wherein the lipid lowering agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, or an ACAT inhibitor.
 - 45. The combination as defined in Claim 44 wherein the lipid lowering agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, itavastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, cholestagel, niacin and/or LY295427.
- 46. The combination as defined in Claim 44 wherein the compound is present in a weight ratio to the lipid25 lowering agent within the range from about 0.001:1 to about 100:1.
- 47. The combination as defined in Claim 37 wherein the antihypertensive agent is an ACE inhibitor, angiotensin II receptor antagonist, NEP/ACE inhibitor, calcium channel blocker and/or β -adrenergic blocker.
- 48. The combination as defined in Claim 47 wherein the antihypertensive agent is an ACE inhibitor which is captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril or moexipril; an NEP/ACE inhibitor which is omapatrilat, [S[(R*,R*)]-hexahydro-6-

[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (gemopatrilat) or CGS 30440; an angiotensin II receptor antagonist which is irbesartan, losartan or valsartan;

- 5 amlodipine besylate, prazosin HCl, verapamil, nifedipine, nadolol, propranolol, carvedilol, or clonidine HCl.
- 49. The combination as defined in Claim 37 wherein the platelet aggregation inhibitor is aspirin, clopidogrel, ticlopidine, dipyridamole or ifetroban.
- 50. A method for treating insulin resistance, hyperglycemia, hyperinsulinemia, or elevated blood levels of free fatty acids or glycerol, hyperlipidemia, obesity, Syndrome X, dysmetabolic syndrome, inflammation, diabetic complications, impaired glucose homeostasis, impaired glucose tolerance, hypertriglyceridemia or atherosclerosis which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a pharmaceutical combination as defined in Claim 43.
- 51. A method for treating irritable bowel

 25 syndrome, Crohn's disease, gastric ulceritis or
 osteroporosis, or psoriasis, which comprises
 administering to a mammalian species in need of treatment
 a therapeutically effective amount of a compound as
 defined in Claim 1.
 - 52. The method as defined in Claim 36 wherein the disease is a liposarcoma or an epithelial tumor.
- 53. The method as defined in Claim 52 wherein the epithelial tumor is a tumor of the breast, prostate, colon, ovaries, stomach or lung.

54. The method as defined in Claim 36 wherein the disease is ductal carcinoma in situ of the breast, lobular carcinoma in situ of the breast, fibroadenoma of the breast, or prostatic intraepithelial neoplasia.